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WARTIME CLINICAL EXPERIENCE WITH THE
TERTIAN MALARIAS OF THE EASTERN MEDITERRANEAN.

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WARTIME CLINICAL EXPERIENCE WITH THE
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This thesis is based on four years experience extending over the whole of the Gallipoli military operations, the Salonika campaign of 1916 with the first nine months of 1917, and finally 18 months in Palestine, Syria, and Egypt. The earlier part was spent with a large General Hospital of 1200 beds in Malta. The latter part was divided between Field Ambulances, sometimes with a temporary fixed hospital as in Jaffa and Tripoli, with a Brigade of the Royal Field Artillery, in a base General Hospital in Alexandria, and finally in the large Demobilisation Camp at Kantara, where the average number in camp was rarely less than 8000 men. Between these various sources an intimate clinical knowledge was gained of upwards of 10,000 cases of tertian malaria, benign and malignant. Advantage was also taken of every opportunity to discuss their experiences with other workers in the same and adjacent fields. Since leaving Egypt in March 1919 I have refrained from reading anything written on the subject of malaria, in order to keep as free from outside suggestion and influence as possible. The thesis contains no reference to books, memoranda, or articles in current medical literature.

In arranging the following notes any detailed

description of a typical malarial attack has been omitted and such is referred to simply as a normal attack. Observations have been grouped under a few convenient general headings, and whilst a certain amount of overlapping and repetition have defied elimination without sacrificing clearness, effort has been made to reduce this potent source of boredom to a minimum. For the same reason brevity has been consistently sought wherever possible. Preference has been given to clinical difficulties, anomalies, and curiosities, with an occasional idea thereby suggested, rather than to systematic setting forth of familiar detail.

Gallipoli. The cases from this front which came under my observation occurred during the latter half of 1915. They were all benign, reacted satisfactorily to quinine, and showed no unusual tendency to relapse or special complication. The total number was very small.

Salonika. The early cases were practically all benign infections from the Struma Valley region. As the hurried precautions taken to control the spread were inadequate, a large proportion of the troops in the district were soon infected, escape being the exception. Crowds of cases poured down to the base hospitals of which the majority were in Malta. Routine quinine administration as understood at that time was carefully carried out. After a short interval it was found that the cases were relapsing to an unexpected degree. It was suggested that this lack of control was due to the

hardness of the sulphate of quinine tablets in general use, with consequent failure of absorption from the alimentary canal. A solution of the sulphate was promptly prepared and its use made compulsory. The relapses continued with undiminished frequency. The next suggestion offered was that the proper salt of quinine was not being employed, so the hydrochloride and bihydrochloride were brought into use. Failure to control the relapses still continuing, recourse was had to the plan of first giving one or more preliminary intramuscular injections before proceeding with the oral administration. Undeterred by persistent failure the enthusiasts finally gave long courses of intramuscular injections combined with the steady administration of massive doses by the mouth. The majority of the cases oscillated uneasily between hospital and convalescent camp, or between Malta and Salonika, according to the onset of the relapses and the available hospital accommodation at the moment. A considerable time elapsed before the partial failure of quinine in malaria was recognised and the new fact accepted that all benign tertians are not of one class, although caused by the same parasites in so far that nothing has yet been discovered to differentiate them except their clinical manifestations. Unfortunately no other drug has been found to exercise any control over the tendency to relapse in these Struma Valley benign infections. Perchance with the rapid advance of medical synthetic chemistry an efficient and satisfactory

remedy will soon be forthcoming. Both in Egypt and since returning home I have seen a number of these unlucky patients, many of whom have had over twenty relapses, still continuing to relapse with correspondingly severe anaemia.

The malignant cases which came later from the same area were more tractable, reacting quickly and satisfactorily to quinine. Cases from the remainder of the Salonika front behaved on normal lines with a fair sprinkling of the usual complications. One noticeable feature was the tendency of benign and malignant infections to occur in alternating groups or waves rather than evenly mixed. In occasional cases the original infection was proved to be benign, but later when cerebral symptoms developed, the crescents of malignant were the only parasites present. The probable explanation was that there had been either a double infection in which the malignant form lay dormant at first and developed later or a secondary malignant infection in hospital. It also raised a hypothetical question whether despite apparent improbability, a benign case might assume in its later manifestations the clinical type of a malignant, and even the parasites undergo a similar metamorphosis.

In Salonika the infection appears to be carried and spread by the mosquitos all the year round, despite the bitterly cold weather during the winter months. This was proved when a number of the 60th. Division landed there from France in December 1916. They had not previously been in any malarial district, yet many of them

developed it by the middle of the following January. The explanation offered was that the infecting mosquitos had been kept alive by the warmth of the huts. It is not altogether satisfactory as sufficiently warm breeding places must have been very scarce indded under such circumstances. (Later in Palestine there was a contrasting difficulty in accounting for the presence of malaria carrying mosquitos during the hot weather in a waterless district.)

The suddenness of the onset of an attack was often remarkable, many of the cases falling out on the march without any premonitory symptoms or rigors. Under these circumstances the diagnosis of heat exhaustion which so frequently accompanied them down to the base was a very natural and excusable one. With few exceptions this class of case proved to be benign tertian when the blood films came to be examined.

Egypt, Palestine, and Syria. Here the type of case gradually changed as the Army proceeded north. On the northern Egyptian coast and in the Canal Zone they were mostly benign. Those before Gaza and later on the line north of Jaffa were similar, though in the latter part of 1917 near Gaza a few malignant cases cropped up, usually of a fulminating cerebral type; and again about August 1918 it was evident that malignant cases were gradually assuming a larger percentage. After the final advance into Syria began, benign cases were a small proportion of the new infections, and from Beyrout and the

Lebanon districts they were almost invariably malignant.

The Jordan Valley early acquired an evil reputation from the health standpoint and supplied a large number of cases, mostly malignant. The anaemia generally prevailing there rendered the attacks much more serious; as a contributory factor this may partly account for the unusually high mortality. They also exhibited a much greater tendency to relapse than the infections from any other Egyptian or Palestinian area, and any accompanying complications always assumed a serious form. Even the natives dread the malaria of this unwholesome district and make an annual migration to the hills during the season when the mosquitos are at their worst.

On all the Eastern fronts the laboratories did magnificent work, often under considerable difficulties, and it is impossible to praise too highly the results they achieved. Like the rest of us they had occasional lapses. One carefully treasured report from the laboratory of a crack colonial General Hospital in Salonika deserves a place in any medical "Punch". The exact reproduction is as follows:- "Bloodsmear positive to " "Malaria Malignant Tertian. Parasites found in great " "numbers in certain fields. In others no organisms " "appear and are found with great difficulty. Numerically " "the ring forms do not appear in sufficient strength " "to diagnose Malignant and are so young on the other " "hand that the possibility of Benign infection must " "not be discarded."

Relapses. The causes of relapse were naturally very difficult to determine accurately. In the majority no definite cause could be assigned. A lowering of the general body tone, such as that brought about by a surgical operation, too prolonged exertion, or alcoholic excess seemed favourable to relapses. Exposure to any extreme of temperature, as the chill caused by too cold a bath, or the heat of a Khemseen wind, was apparently a definite reason in some cases. Mental or emotional stress was at times clearly indicated, being traceable to bad news received from home, or to being informed of an early return to the trying conditions of the front line. Making every allowance for coincidence and a certain inevitable amount of malingering a considerable residue of genuine cases remained. A marked and to me unexpected feature was the rapidity with which the onset of pyrexia followed the apparent exciting cause. In my own personal case, a malignant acquired in Syria while with the Artillery chasing the Turks during General Allenby's last advance north, a too cold bath taken at 10 a.m. was followed by a rapid rise of temperature about 4 p.m. There were other cases where the distribution of a mail gave a definite time to the determining factor, and the relapse occurred within 8 hours. A noticeable number of cases relapsed at about 10 day intervals, and when the expected relapse did not occur it happened after a further 10 days. Contrary to my preconceived ideas, cases exhibited less tendency to

relapse on being transferred to a cooler climate, while on remaining in an equally warm or warmer climate in a different zone they relapsed with the same freedom as in the place of original infection. Exposure to the sun was frequently blamed as a cause of relapse, but the possibility of exhaustion as a contributory factor must not be lost sight of.

It would appear that the resting form of the parasite can lie dormant for an indefinite period without losing its vitality. Cases have been known to relapse after ten years residence where mosquitos were nonexistent and a fresh infection impossible. Where its favoured locus may be situated during the resting periods remains a doubtful point which requires a specially conducted investigation to clear up. Once that nidus is found, there is good ground for hope that science will be capable of bringing some adequate agent to bear on it with satisfactory results.

After one or more relapses the symptoms of an attack usually began to depart from the normal type in that the rigor would be absent, the hot and sweating stages much modified, and the patient's chief complaints confined to malaise and headache. No symptom could be relied on to be invariably present, but only in rare instances was the headache absent.

Complications, especially jaundice, were as frequent during relapses as with the primary attacks. A normal uncomplicated original attack was no guarantee that

subsequent relapses would be similarly free.

Anaemia. The destruction of the red corpuscles by the parasites made anaemia a symptom of every case. The degree varied from a very slight to a profound anaemia, giving on testing an index as low as 50 % Hb. It was most severe where there had been a series of relapses or when pyrexia had been unusually persistent. If free from relapse the benign cases regained a normal haemoglobin standard more rapidly than the malignant. Iron was often prescribed alone or in combination with Arsenic, but no proof was adduced that any benefit was derived from its use. On the other hand it occasionally upset the digestive functions: a practical disadvantage outweighing any hypothetical gain. It was most satisfying to a thoroughgoing oldfashioned belief in the natural recuperative powers to find within the short space of a week that an anaemia with a 60% Hb. index had changed to a full 100% with no other treatment than rest in bed and plenty of good nourishing food. Such cases were by no means rare.

Loss of adhesiveness was a peculiar quality in the blood of many of these advanced anaemias, so that the greatest possible care had to be used in staining the films to prevent the blood washing off the slides. I have heard no explanation of this unusual behaviour, though it may indicate that the malarial parasite has some other action on the blood than merely breaking up the red cells it uses as host.

Splenic Enlargement. Even after several relapses appreciable enlargement of the spleen did not occur with the frequency one had been led to expect. Allowance must be made for the personal equation of the clinician, as it was a common experience for me to be unable to detect slight degrees of enlargement which were palpable to other competent observers. A persistent dull pain over the splenic area, increased on movement or jolting, was a reliable indication of easily discernible enlargement. On the other hand definitely palpable swellings often gave no pain. Provided there were no further relapses the spleen resumed its normal size gradually, in some cases rapidly. I noted a greater proportion of enlarged spleens, usually free from pain, amongst our Indian contingents than amongst the White troops. This accords with what might reasonably have been expected, as so many of them had previously had attacks in India and Mesopotamia before coming to Palestine.

Jaundice. Whilst this was comparatively rare in the Salonika cases it occurred commonly among those arising in Palestine and Syria, especially from the Jordan Valley. It was the most frequent of the various complications and accompanied both benign and malignant. That of the benign form was transient, generally disappearing within a week. That of malignant was often profound and usually tedious, lasting six or more weeks. A large percentage of these jaundiced cases had no other symptoms, did not feel ill except general weakness, and had no history of pyrexia or rigors. As a

rule the convalescence of jaundiced patients was more prolonged than with other complications. Different drugs were tentatively tried to hasten the resolution of the icteric condition but no markedly beneficial results could be ascribed to any of them.

Cerebral Involvement. The cerebral cases were all malignant infections. They frequently developed alarming symptoms without previous warning, and immediate active treatment was necessary if life was to be saved.

Illustrating the peculiar onset of some of these cases, it happened on more than one occasion in Syria that the first intimation of a cerebral attack was a message that a man had "suddenly gone wrong in his head."

Inquiry elicited no evidence of previous symptoms, and the temperature was rarely over 101 which is low for the beginning of a malarial attack in that district. There followed a rapid transition from rambling delusions to a muttering delirium, disproving any idea of insanity and suggesting cerebral malaria. My own experience was that an intravenous injection of 15 grains of the quinine hydrochloride alleviated the worst symptoms, and all that was necessary afterwards was to proceed with oral administration of a solution of the sulphate, giving 30 grains daily for a month, when the treatment could be safely discontinued. Blood films from these cerebral cases were apt to be peculiarly deficient in parasites, thereby increasing the difficulty of making a differential diagnosis from other cerebral

conditions, the more so as we had become gradually bound hand and foot to laboratory assistance before venturing a decision. It was contrary to orders to make a definite diagnosis of malaria until the parasites were reported present in the blood films: their returns were an ever present nightmare to the official minds.

Diarrhoea. A rather frequent complication of cases from all these fronts was a profuse bloody mucoid diarrhoea, with less straining and tenesmus than a typical dysentery, but in which the laboratory experts were unable to detect any of the usual amoebae or bacteria causing that disease. As all these areas were prolific in genuine dysenteries there was always a doubt whether the diarrhoeic complication was not really such, brought about by the lessened resistance of the bowel to the aforesaid agents; especially as practically everybody who lives in the East is temporarily a carrier. This was demonstrated at one hospital where to fill up an interval of slackness in the work it was determined to test and so weed out of the cooking kitchens any men who might be found to be dysentery carriers. The first rough test gave over 60% carriers, after which eye opener further investigation was abandoned. Had the tests been completed it would probably have been found to be the exception not to act as host to these ubiquitous germs in tropical and subtropical countries.

Where calomel was given as a preliminary to quinine in cases of malarial diarrhoea it was found that the

haemorrhage was increased. This suggests a practical rule that caution should be exercised before giving calomel in any case of intestinal haemorrhage.

Since demobilisation I have seen two cases of malarial relapse (places of origin, Salonika and Mesopotamia) accompanied by a clear mucoid jelly-like diarrhoea, free from any trace of blood, and without tenesmus or pain. Blood films proved they were benign tertian. Neither had any history of dysentery, and their stools contained no dysenteric germs or cysts.

Pneumonia. This was a rare complication during the first three years, but in 1918 and especially the latter half of that year it was frequent and very fatal. There was again a difficulty in deciding whether it might not be that the patient was coincidentally suffering from influenza, in which particular epidemic of that disease pneumonia was a frequent complication. During October 1918 the experiment was made at the large fixed hospital of the Tripoli Casualty Clearing Station of examining blood films from 50 typical influenzas. Malarial parasites were found to be present in large numbers in over 40 of the cases. That these pneumonias derived little or no benefit from quinine seems rather to favour the view that the pneumonic trouble was not an integral part of the malaria.

Nephritis. This was at times found in malarial patients particularly from Salonika. There was always a certain proportion of nephritics amongst the troops, and so many

men had been in areas where an infective nephritis was rife, that it was hardly justifiable to definitely assume any direct relationship between the two diseases occurring in the same case. A negative assumption is also out of court because in the organs known to be selected by the malarial parasite, as the brain and liver, the result is largely due to blocking of the capillaries, and the kidney has an equally good vascular supply.

Blackwater Fever. The proportion of these cases was less than .1%, occurring at irregular intervals on all the Eastern fronts. It was more common amongst benign than malignant infections, probably due to the greater tendency of the benign of those regions to relapse. Every blackwater fever had previously had several malarial relapses. The usual and most successful treatment was intramuscular injection of the bihydrochloride of quinine which in my experience always cleared up the attack in a few days. I have heard of fatal terminations but have never seen one; its reputation appears worse than it deserves.

Apyrexial Cases. Although the possibility of the occurrence of apyrexial cases is denied by many clinicians, I have a distinct suspicion that such cases may happen. Perchance the malaise and other symptoms may be so trifling at their first onset as not to attract attention, and so a slight rise of temperature may be overlooked. Two classes of cases cropped up from time to time in

which it was impossible to get any history of pyrexia or of rigors. One type arrived at the base with a diagnosis of jaundice, had no history of pyrexia, no rise of temperature in hospital, but the peripheral blood contained numerous crescents of malignant. The other type complained chiefly of muscular and joint pains, and arrived with a label of "myalgia". As this usually occurred in men of about 40, who would reasonably expect to be invalided home if their illness were a prolonged one, it raised a doubt whether there might not be an element of malingering. The discovery of the parasites of benign was again irrefutable evidence that malaria was present and possibly the cause of the symptoms.

When considering the protean forms which malaria can assume, sight must never be lost of its tendency to relapse as a complication of any disturbance of the body mechanism. If it be admitted (and it seems beyond question) that a slight operation, a chill, or a mental upset can cause a speedy relapse, surely there is no stretching of the probabilities in suggesting that the development of influenza, pneumonia, or one of the typhoid group of diseases, even in their prodromal stage, can produce a similar result. Unfortunately the natural desire to score off somebody else produced a tendency for anyone finding a definite laboratory result differing from the original diagnosis to immediately assume a previous error and make a report reflecting on the care with which the work was done up the line. One

heard strangely little of mixed infections although they must have been numerous under the prevailing conditions.

Treatment. During the earlier part of the war each Hospital Unit was allowed a practically free hand in the methods of treatment it adopted. Much useful information was thereby obtained which would otherwise never have come to light. It was clearly shown that it is possible to give much larger doses of quinine continuously over a prolonged period than had ever been given before, without any troublesome toxic symptoms appearing. Almost the only noticeable evidences of toxicity were deafness sometimes accompanied by tinnitus, and disturbance of the cardiac rhythm with or without tachycardia. These unpleasant effects were temporary, passing away gradually when the quinine was discontinued. One case inadvertently received 180 grains orally and 30 grains intramuscularly within 12 hours without any marked ill effects. As previously mentioned, some of the Hospitals tried massive doses over long periods on finding small doses ineffectual in controlling the tendency to ~~re~~ relapse in the Struma Valley benign infections. When one General Hospital was moved from Malta to Salonica upwards of 250 cases of malaria were transferred to the Hospital in which I was working as Medical Divisional Officer. They were accompanied by unusually complete case papers and temperature charts, affording ample opportunity of studying them in detail. Doses of 15 to 20

grains intramuscularly each second day, combined with 60 to 90 grains orally daily continued for three and in cases six months were frequent, the patients relapsing repeatedly at uncertain intervals. One was left wondering whether to be more staggered by the dogged heroism of the Patients, the unswerving faith in Quinine of the Medical Officers, or the futility of it all as evidenced by the recorded results. They at least proved that Blackwater Fever is not the result merely of taking large doses of quinine over long periods as has been suggested, because no cases were recorded at this Hospital amongst so many massive doses. At the same time it would be rash to conclude that in rare cases quinine may not be the determining factor of a "blackwater" attack without being the actual cause. Such at least was the belief of some of the Medical Officers working in German East Africa, where this complication appears to have been more prevalent. It is premature to come to a definite decision until the clinical results from all the Fronts have been collated and critically examined. That a temporary tachycardia and arrhythmic heart action could be caused by quinine was largely overlooked, with the result that many men were unfortunately labelled as suffering from heart mischief, and their services in the front line were unnecessarily lost. Even though these cases came up again for revision, Medical Boards were naturally chary of altering any definite diagnosis of heart trouble.

It was found a sound practical working rule to give quinine in all cases where the diagnosis was doubtful, or where the treatment appropriate to the apparent disease was not producing satisfactory results, and to ignore any laboratory report where the malarial parasite was not found in the peripheral blood.

Intramuscular Injections. Considering the enormous number of these injections which were given, the proportion of untoward results was gratifyingly small. Very few were followed by abscess formation, which is high testimony to the efficient precautions taken in sterilising. Healing followed a normal though tedious course. A small number had been inserted too near a nerve trunk and were followed by corresponding local wastings, fortunately of a temporary character. In the rare cases where the injection had not been sufficiently deeply inserted to enter the muscle substance, a circular superficial slough formed with sharp edges looking as if the skin had been punched out. These sores were very resistant to ordinary treatment and sometimes excision of the area was requisite before satisfactory healing could be secured. Lastly, cases occurred at intervals in which the injection appeared to become encysted, the part remaining extremely painful, and a firm round swelling was palpable at the point of injection. When this was aspirated a clear straw coloured fluid containing quinine was drawn off, but in which microscopy and cultivation alike failed to show any microbic

infection. In my case three intramusculars were given a short distance below the iliac crests. There were no signs of septic infection and no local irritation, yet those points were painful to slight pressure for at least four months, and so far as could be ascertained absorption was exceedingly slow, much resembling the resolution of an organised haematoma.

A certain number of cases (apart from the Struma Valley infections) cropped up regularly in which despite a preliminary purge and hepatic stimulant there was no reaction to quinine given orally. One intramuscular injection was usually found sufficient to establish the action of the drug, after which oral administration could be satisfactorily proceeded with. Only in very rare cases was it necessary to give more than one intramuscular, though latterly in Egypt it was the official routine treatment to give three to six such injections before proceeding with quinine solution by the mouth.

Intravenous Injections. These were only used in cerebral cases and gave curiously different results in Malta and Palestine. In Malta the only plan found beneficial was to immediately give an intravenous injection of 10 to 15 grains of the hydrochloride. In Palestine this method gave such unsatisfactory results (one might almost say "fatal results"), as to be practically abandoned in favour of the intramuscular route. As the same dosage and salt of quinine were employed in both

instances it is difficult to explain the remarkable discrepancy. The bihydrochloride was not generally considered equal in efficiency to the hydrochloride. The sole difficulty encountered in intravenous administration was the exceptionally small lumen of the veins found in some arms, necessitating a careful dissection before the injection could be satisfactorily proceeded with.

In 1915 and 1916 it was customary to withhold the giving of quinine until a blood film proved positive, in the belief that its administration caused the parasites to disappear and so obscured the diagnosis. Later experience showed that this was not so in the bulk of cases, but rather that their number was diminished and more careful searching of the films was required. This partial failure of quinine to completely eliminate the parasite raises the query as to how the drug exercises such a wonderfully beneficial action in most cases. Possible explanations are that whilst it does not kill the parasite, it may be destructive to or neutralise the toxins produced; or may act as an antidote to them; or may bring about a condition of the blood which is unfavourable to the development of both parasite and toxins. The last suggestion may well be at least a part of the truth. The reduction in the tendency to relapse brought about by removal to a cooler climate may be similarly due to the production of a blood condition inhibiting the growth and activity of

the parasite. The varied character and slighness of the causes which can bring about a relapse, and the rapidity with which it follows the application of the stimulus suggest that the mechanism regulating the inhibition is an exquisitely delicate one. If it be permissible to stray into the realms of pure guessing, three hypotheses as to the character of this inhibiting mechanism may be hazarded:-

- (1) That it does not depend on the production of antibodies or other definite complex chemical compounds.
- (2) That it may depend partly on some slight adjustment of balance of the normal blood ingredients.
- (3) That whatever other factors exercise control, it also depends on some educative effect on that elusive but ever present quality of vital resistance to harmful agencies which is the common inheritance of all life.

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